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On the use of fractional order PK-PD models

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Abstract. Quantifying and controlling depth of anesthesia is a challenging process due to lack of measurement technology for direct effects of drug supply into the body. Efforts are being made to develop new sensor techniques and new horizons are explored for modeling this intricate process. This paper introduces emerging tools available on the 'engineering market' imported from the area of fractional calculus. A novel interpretation of the classical drug-effect curve is given, enabling linear control. This enables broadening the horizon of signal processing and control techniques and suggests future research lines.

1. Introduction

The emerging concepts of fractional calculus (FC) in biology and medicine have shown a great deal of success, explaining complex phenomena with a startling simplicity ([1, 2, 3]). It is clear that a major contribution of the concept of FC has been and remains still in the field of biology and medicine ([4]). Fractional calculus generously allows integrals and derivatives to have any order, hence the generalization of the term *fractional-order* to that of *general-order*. Of all applications in biology, diffusion is the one most appealing from modeling point of view, since it allows characterizing a relatively complex process with parsimonious models.

Modeling drug dynamics in the body using compartmental models is perhaps one of the most popular modeling approach ([5]). These models are based on mathematical characterization of molecular biochemistry and transport phenomena in the body ([6]). As such, diffusion plays an important role in drug assimilation, transport and clearance, and it is a physiological process which can be well described by means of fractional calculus ([7]).

In this paper, a fresh view upon the models for drug release and their effect will be given in the application of depth of anesthesia regulation. If one would like to have optimal drug infusion rates into a patient with avoiding over- and under-dosing, then accurate patient models are necessary (although not sufficient, since a good control methodology is also required) ([8]). Accurate models may hold a realistic dynamic perspective for average populations datasets, but they are by far sub-optimal when patient-individualized control is envisaged. This is due to the fact that inter-patient variability has a strong impact on the perception and effectiveness of the drug into the body of the patient (i.e. drug effect, patient sensitivity to the drug, etc). A schematic representation of the anesthesia paradigm in terms of its components is given in figure 1. The hypnosis and neuromuscular blockade are well-characterized, yet the analgesia component remains challenging for control purposes because no direct output measure is available. Hence, no specific models are yet available for analgesia effect in the human body during general anesthesia (i.e. unconsciousness). The pharmacokinetic (PK) models available in the literature are linear in

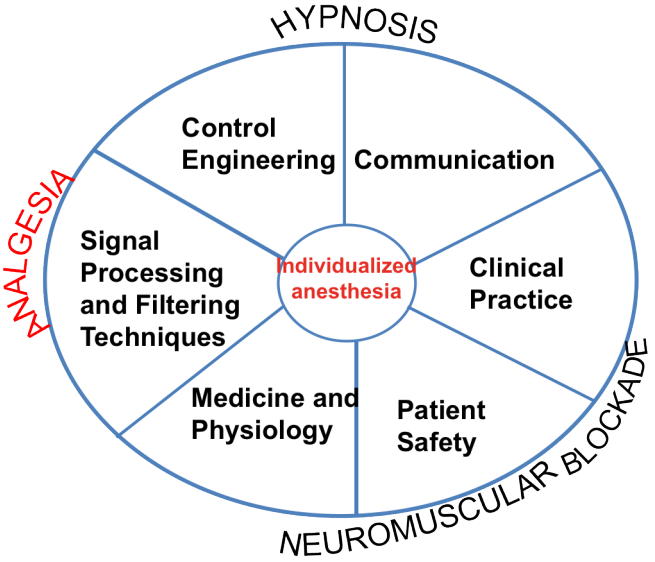

Figure 1. A personal view of the anesthesia paradigm. The items in red are the current challenges.

terms of model parameters and dynamics ([9, 10]). Their frequency response is quasi-identical, less for a scaling factor in the gain (i.e. this accounts in part for the sensitivity to the drug with respect to the body mass index of the patient). The pharmacodynamic (PD) models, are usually represented by nonlinear Sigmoid (Hill) curves and represent the relationship of the drug concentration to the drug effect in each patient. From patient-individualized control point of view, PD models are the most challenging part of the patient model and pose most challenges for control (i.e. highly nonlinear characteristic).

Fractional calculus offers tools to model such nonlinear characteristics as those of the PD models with less degree of nonlinearity in model parameters ([3]). The original purpose of this paper is to show a methodology which enables a different, fresh view to these models and how they can be integrated in the control paradigm of depth of anesthesia regulation.

The paper is structured as follows: next, a brief introduction on the fractional calculus tools for modeling drug release and its effect is given. Section III depicts the classical methodology for PK-PD models in anesthesia and section IV presents the proposed PD modeling approach and some simulation results. Current limitations for the use of these models in a closed loop control paradigm are given and a conclusion section summarizes the main outcome of this paper.

2. Tools from fractional calculus

Pure empirical models such as input - output models are rather descriptive with loss of physiological insight into the drug absorption, transport, diffusion and release. However, from control point of view they are the most simple to obtain and to deliver information to the controller for deciding the optimal drug infusion rate necessary for the specific patient whose model is available. On the other hand, physiologically and bio-chemically based models are difficult to attain due to the extraordinary complexity of this process. An intermediate solution is perhaps the use of semi-empirical models. Such a model which is fairly simple to employ in characterizing drug release is the power-law model:

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t and M_∞ are cumulative amounts of drug released at time t and infinite time, respectively; and k is a constant reflecting the structural and geometrical characteristics of the system, and n is the so-called "release exponent" ([11]). For purely diffusion-controlled release, $n = 0.5$. other values of n may be indicative of various diffusion conditions. These features of this model are of special interest in our study since we would like to look at the inter-patient variability from this standpoint.

Following the fundamental law of physics which applies to well stirred, homogeneous systems, it follows that the mean square displacement of the walker, $< x^2 >$ in the random walk model is proportional to time ([12, 13]):

$$< x^2 > \propto t \tag{2}$$

However, in disordered systems, such as most biological environments, this is no longer proportional with time, but with the fractal walk dimension of the walker:

$$< x^2 > \propto t^{D_w} \tag{3}$$

with $D_w \neq 2$. This property implies that scaling laws such as power laws are associated with kinetics of various processes taking place in the (biological) environment (i.e. tissue). Most biological tissues can be approximated in their properties by polymers. As such, the spatio-temporal porosity of a dynamically changing polymer is close to the percolation threshold for non-classical diffusion effects impinging on release kinetics. Fractional calculus has shown in several (non)biological applications that classical diffusion as well as non-classical diffusion can be characterized by fractional order differ-integrals models ([4]). It is therefore simple to derive further the model from (1) in its Laplace equivalent. Consider that the amount of drug released varies in time and that the amount released at infinite time is a constant. This results in the following Laplace domain model equivalent:

$$\frac{M_t(t)}{M_\infty} = k\frac{\Gamma(1-n)}{s^{1-n}} \tag{4}$$

where Γ is the Gamma function and s the Laplace operator. If a step input is applied to this model, i.e. apply a constant drug infusion rate, one obtains:

$$\frac{M_t(t)}{M_\infty} = ks^n\Gamma(1-n) \tag{5}$$

which is then a fractional order model (more information about such models is given in *Appendix*). This result has regained the attention of the research community and current efforts are being directed towards providing pharmacokinetic models with fractional order differ-integrals ([14, 15]).

3. Classical PK-PD models

In order to control the depth of sedation based on predictive control strategies, a model which captures the dynamics of the patient is required. The selection of the model input and output variables is crucial for optimal control. Propofol is a commonly used hypnotic drug to induce general anesthesia ([8]). Using the electroencephalogram (EEG), several derived, computerized parameters like the BIS have been tested and validated as a promising measure of the hypnotic component of anesthesia. BIS values lie in the range of 0-100; whereas 90-100 range represents fully awake patients; 60-70 range and 40-60 range indicate light and moderate hypnotic state, respectively ([16]).

PK-PD blocks denote compartmental models. The PK-PD models most commonly used for propofol and remifentanil are the 4th order compartmental model described by Schnider ([9, 10])

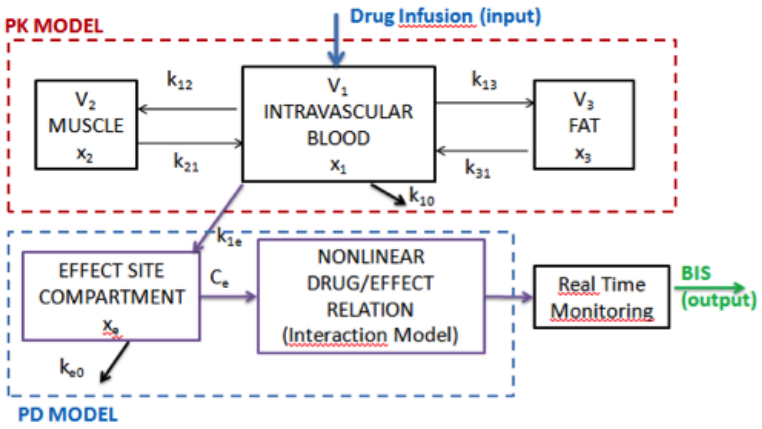

Figure 2. General compartmental model of the patient, where PK denotes the pharmacokinetic model and PD denotes the pharmacodynamic model of an infused drug.

and they have the structure depicted in Fig. 2. In this figure x_1 [mg] denotes the amount of drug in the central compartment. The blood concentration is expressed by x_1/V_1. The peripheral compartments 2 and 3 model the drug exchange of the blood with well and poorly diffused body tissues. The masses of drug in fast and slow equilibrating peripheral compartments are denoted by x_2 and x_3, respectively. The parameters k_{ji}, for $i \neq j$, denote the drug transfer frequency from the j^{th} to the i^{th} compartment and $u(t)$ [mg/s] is the infusion rate of the anesthetic drug into the central compartment. An additional hypothetical effect compartment was proposed to represent the lag between drug plasma concentration and drug response. The concentration of drug in this compartment is represented by x_e. The parameters k_{ij} of the PK models depend on age, weight, height and gender and the relations can be found in [9, 10].

The PK-PD model is represented by the following equations:

$$\begin{aligned} \dot{x}_1(t) &= -(k_{10}+k_{12}+k_{13})\cdot x_1(t) + k_{21}\cdot x_2(t) + +k_{31}\cdot x_3(t) + u(t)/V_1 \\ \dot{x}_2(t) &= k_{12}\cdot x_1(t) - k_{21}\cdot x_2(t) \\ \dot{x}_3(t) &= k_{13}\cdot x_1(t) - k_{31}\cdot x_3(t) \\ \dot{x}_e(t) &= -k_{e0}\cdot x_e(t) + k_{1e}\cdot x_1(t) \end{aligned} \tag{6}$$

The effect compartment receives drug from the central compartment by a first-order process and it is regarded as a volumeless additional compartment. Therefore, the drug transfer frequency from the central compartment to the effect-site compartment is equal to the frequency of drug removal from the effect-site compartment: $k_{e0} = k1e = 0.456\ [min^{-1}]$. The corresponding concentration in the effect site compartment is denoted by C_e. The parameters k_{ij} of the PK models depend on age, weight, height and gender and can be calculated for Propofol:

$$\begin{aligned} &V_1 = 4.27[l]; V_2 = 18.9 - 0.391(age-53)[l]; V_3 = 2.38[l]; \\ &Cl_1 = 1.89 + 0.0456(weight-77) - 0.0681(lbm-59) + 0.0264(age-53)[l/min] \\ &Cl_2 = 1.29 - 0.024(age-53)[l/min]; Cl_3 = 0.836[l/min]; \\ &k_{10} = \frac{Cl_1}{V_1}[min^{-1}]; k_{12} = \frac{Cl_2}{V_1}[min^{-1}]; k_{13} = \frac{Cl_3}{V_1}[min^{-1}]; \\ &k_{21} = \frac{Cl_2}{V_2}[min^{-1}]; k_{31} = \frac{Cl_3}{V_3}[min^{-1}]; \end{aligned} \tag{7}$$

where Cl_1 is the rate at which the drug is cleared from the body, and Cl_2 and Cl_3 are the rates at which the drug is removed from the central compartment to the other two compartments by distribution. The lean body mass *(lbm)* for women and men are: $lbm_{men} =$

$1.1 \cdot weight - 128 \cdot \frac{weight^2}{height^2}$ and $lbm_{women} = 1.07 \cdot weight - 148 \cdot \frac{weight^2}{height^2}$, respectively. The relation between the effect site concentration C_e and the BIS is given by a nonlinear sigmoid Hill curve:

$$BIS(t) = E_0 - E_{max} \cdot \frac{C_e^{\gamma}(t)}{C_e^{\gamma}(t) + C_50^{\gamma}} \tag{8}$$

where E_0 is the BIS value when the patient is awake; E_{max} is the maximum effect that can be achieved by the infusion of Propofol; C_{50} is the Propofol concentration at half of the maximum effect and γ is a parameter which together with the C_{50} determines the patient sensitivity to the drug. E_0 and E_{max} are usually considered equal to 100.

As explained earlier, the main challenge for control standpoint is the nonlinearity of the Hill curve given by (8) and the inherent inter-patient variability. To illustrate this to the reader, a realistic set of typical and atypical patients has been used, with the parameter values given in Table 1. The resulted Hill curves by simulating the PKPD model of these patients is shown in figure 3.

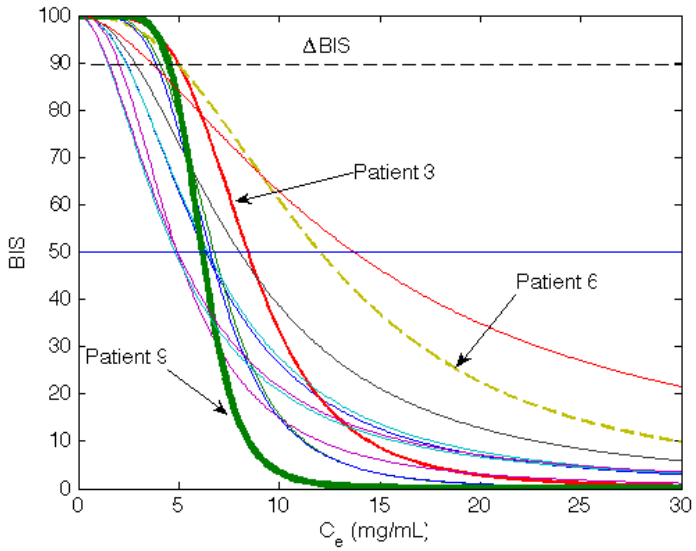

Figure 3. Example of Hill curves from various patients.

4. Proposed Modeling Approach and Analysis

Recall that the equation (1) is the basis for the fractional order model from (5). As explained, the red-line connecting these models is based on the theory of fractional calculus and fractal walk dynamics. An interesting feature of systems characterized by fractal dynamics is the following: represented on a log-log plot, their characteristic becomes linear. This feature is of special interest for us, especially if the reader may recall the Hil curve from figure 3. Of course, it would be very nice if the strong nonlinearity and inter-patient variability depicted in this figure would be diminished, or even better, simply vanish into thin air. In this section, some ideas will be put forward which will lead the reader through this new approach of viewing Hill curves for drug effect to concentration relationship.

Based on (1) one can write the same relationship for the Hill curve:

$$\frac{BIS(t)}{Ce(t)} = k \cdot t^n \tag{9}$$

Patient	Age	Length	Weight	Gender	C_{50}	E_0	E_{max}	γ
1	40	163	54	F	6.33	98.80	94.10	2.24
2	36	163	50	F	6.76	98.60	86.00	4.29
3	28	164	52	F	8.44	91.20	80.70	4.1
4	50	163	83	F	6.44	95.90	102.00	2.18
5	28	164	60	M	4.93	94.70	85.30	2.46
6	43	163	59	F	12.10	90.20	147.00	2.42
7	37	187	75	M	8.02	92.00	104.00	2.10
8	38	174	80	F	6.56	95.50	76.40	4.12
9	41	170	70	F	6.15	89.20	63.80	6.89
10	37	167	58	F	13.70	83.10	151.00	1.65
11	42	179	78	M	4.82	91.80	77.90	1.85
12	34	172	58	F	4.95	96.20	90.80	1.84

Table 1. Characteristic variables for each of the virtual realistic 12 patients used in this study.

where k and n are varying on the patient PK-PD characteristics. If one compares (8) with (9) it can be recognized the resemblance in the power term and observe in fact a simplification of the model from (8) in terms of parameter number. From a structural point of view, there is no difference between the models, since both are semi-empirical models. The term $\frac{BIS(t)}{Ce(t)}$ denotes the effect-to-concentration ratio (ECR) and its units are [%/mg/ml]. Based on the principles of fractal walk, if the scale of the ECR representation is changed from linear to logarithmic, it becomes a (quasi)linear relation.

To verify whether the ECR becomes (quasi)linear, one may calculate the drug effect $BIS(t)$ as a function of the drug concentration $Ce(t)$. The profile of $Ce(t)$ may differ depending on the type of depth of anesthesia regulation that can occur in practice. Usually, in target-controlled infusion systems, drug is infused in the patient in open loop (i.e. no feedback from the patient is explicitly taken into account !) and is the most widely applied in clinical practice. Averaged population models are used to predict the concentration in the blood and thus in the effect site compartment from (6) and their corresponding BIS effect. If we would represent this in time, it appears as a train of steps of different values; i.e. the anesthesiologist changes the value of the targetted concentration depending on the reactions in biological signals from patient (e.g. heart rate, respiratory rate, blood pressure, cardiac output, oxigen concentration, etc).

There are three profiles investigated in this paper: i) a linearly increasing concentration, ii) a first order lag and iii) a second order lag, as in figure 4. of course, in practice, the time constant of the concentration profiles is much larger than the one taken in this example. However, this does not affect the overall conclusions. Figure 5 plots the evolution of ECR with these three variation characteristics of Ce, for an averaged population of data from table 1.

Notice that in figure 5 both X and Y scales are logarithmic. Observe that the ECR is indeed quasi-linear and that the difference in slope is attributed to the variations in the dynamic profiles of Ce. if one repeats this simulation using all the values from the table 1, one obtains the result given in figure 6. An interesting result is that of moving the effects of inter-patient variability at *later times*. This allows to *postpone* the robustness check of the controller with respect to variations in the model. This allows performing online identification for attaining a specific model of the respective patient during general anesthesia, thus updating the model parameters in-between the control samples. A possible method for this patient-individualized control of anesthesia is given in [17].

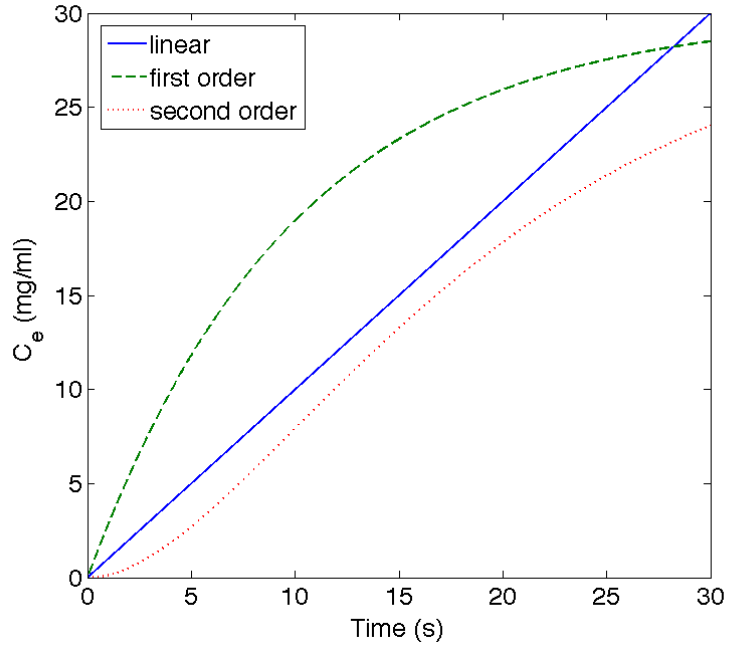

Figure 4. Example of *Ce* curves for an averaged patient model parameter values based on table 1.

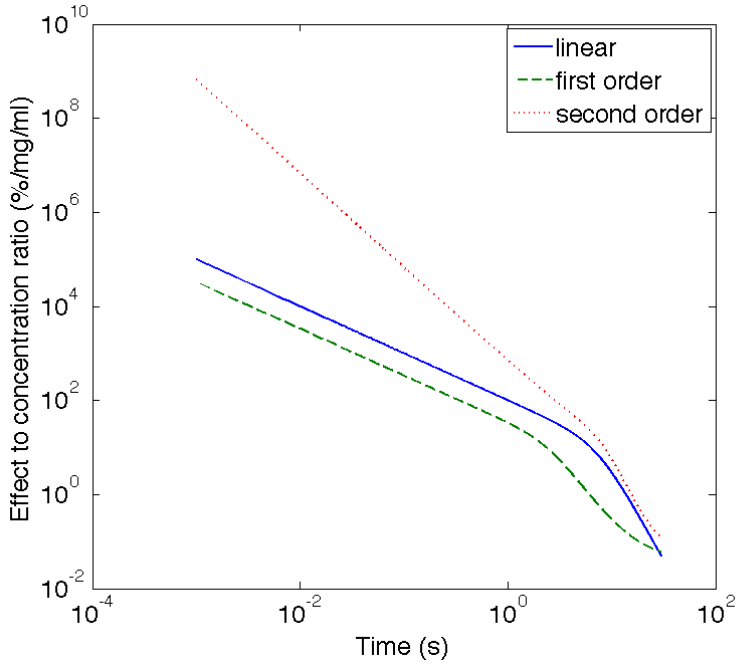

Figure 5. Example of ECR curves for an averaged patient model parameter values based on table 1.

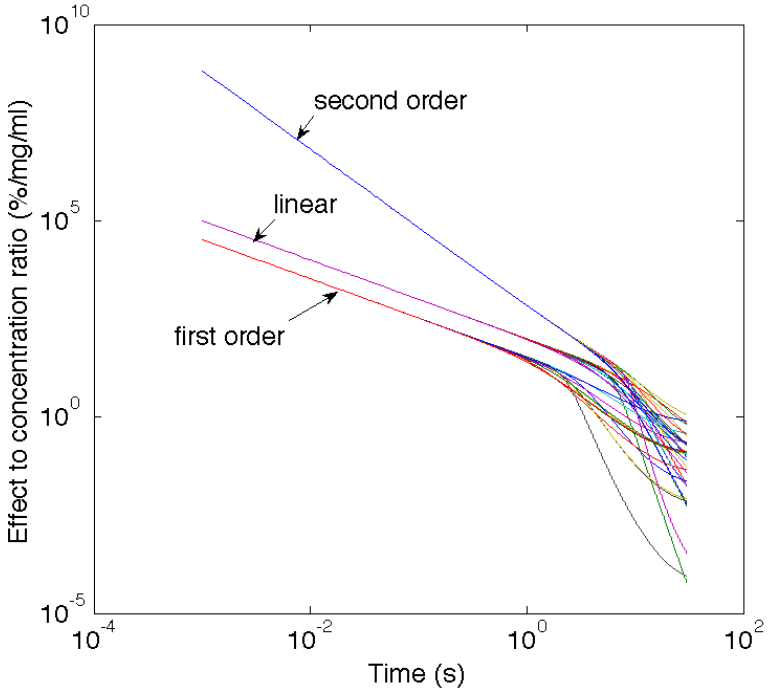

Figure 6. Example of ECR curves for all patient model parameter values from table 1.

To show the efficiency of fractional order operators simulation results for a PKPD model presented in section 3 are depicted in figure 7 depicts the time evolution of the Propofol amount for different values of n: $n = 0.6; 0.8; 1.0$.

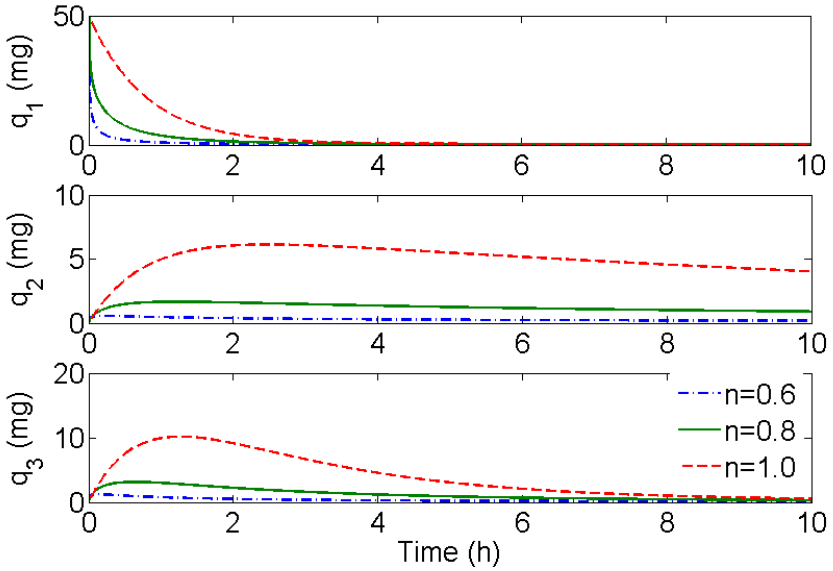

Figure 7. Propofol amount as a function of time for compartment 1, compartment 2 and effect site compartment.

The model coefficients have been calculated for a male person of 74 years old, 88 kg, 164 cm and a bolus injection of 50 mg injected at a rate of 3.3. mg/s during 15 seconds. It can be observed that for $n = 1$ the patient is more sensitive to the drug than for $n = 0.6$. A higher amount of drug is diffused in the muscle and effect compartment, resulting in lower values of the BIS signal. This is in part due to the fact that a value for $n = 1$ will imply a normal diffusion process, whereas for $n < 1$ a sub-diffusion occurs, the drug being faster cleared out of the body (less uptake). For $n = 0.6$ less drug uptake occurs, the effect is limited and values do not reach sedation, i.e. effect remains above 50%.
Our results suggest that the proposed fractional order compartmental model captures well inter-patient variability since different values of n can lead to slower or faster uptake and various effects.

5. Current Limitations

If the same constant drug infusion rate would be given to all patients from table 1, then the result depicted in figure 8 will be obtained in terms of $BIS(t)$ output variation with time. It is

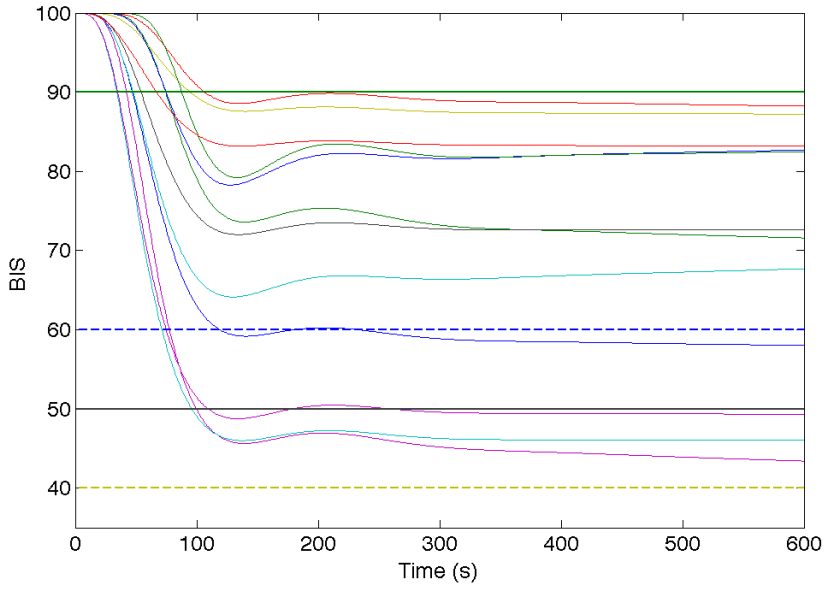

Figure 8. Example of BIS curves resulted from a constant drug infusion rate for all patient model parameter values from table 1.

therefore obvious that i) closed loop control is necessary and ii) an averaged patient model will deliver sub-optimal results since they require a robust, conservative controller able to deal with the inter-patient variability. Moreover, it is also clear that the inter-patient variability may vary quite significantly and that one single controller (without online adaptation) will never suffice in practice. A first problem is to find online adaptation algorithms which may adapt the model parameters k and n to the patient characteristics. Identification from logarithmically sampled data has been proposed in ([18]) and represents a good framework for developing the online identification algorithm.

The next problem is to find a solution to integrate the model from (9) into a closed loop control system taking into account the requirement for a logarithmic sample time (i.e. in order to maintain linearity). Although it may look surprisingly, it has already been shown in various examples that a Riemann sampling rate (i.e. linear periodic) may be outperformed

by a Lebesque sampling rate (i.e. event-triggered) in several applications ([19]). Since the Lebesque sampling rate is an event triggered rate used successfully in practice in closed loop control (e.g. networked control, sensor networks), it may be revealing to look into the possibility of a logarithmic sampling rate.

6. Conclusion

This paper presented the available tools emerging from fractional calculus to model the nonlinear characteristics of the pharmacokinetic and pharmacodynamic patient models. Advantages and challenges have been discussed. Results suggest that the high degree of inter-patient variability and nonlinearity may be avoided, leading to linear control techniques instead of advanced, complex control techniques.

Further steps of this research line are dealing with the current limitations: i) online identification of logarithmically sampled data and ii) control of logarithmically sampled systems.

7. Appendix

The fractional calculus is a generalization of integration and derivation to non-integer (fractional) order operators ([20, 21]). First, we generalize the differential and integral operators into one fundamental operator D_t^n (n the order of the operation) which is known as *fractional calculus*.

Several definitions of this operator have been proposed, mainly based on generalization of

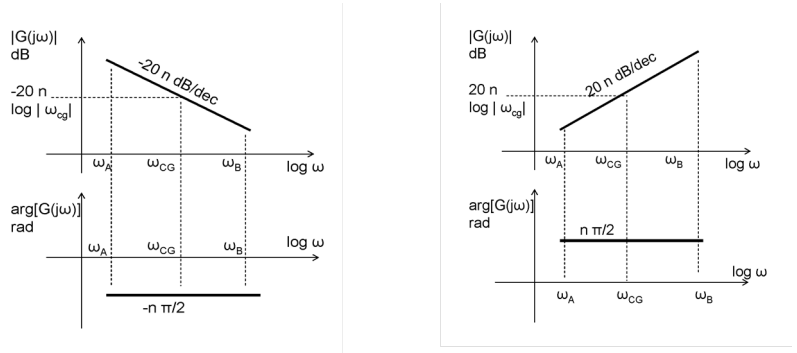

Figure 9. Sketch representation of the FO integral and derivator operators in frequency domain, by means of the Bode plots (magnitude above and phase bellow).

the standard differential–integral operator in two main groups: (a) they become the standard differential-integral operator of any order when n is an integer; (b) the Laplace transform of the operator D_t^n is s^n (provided zero initial conditions), and hence the frequency characteristic of this operator is $(j\omega)^n$. The latter is very appealing for the design of parametric modeling and control algorithms by using specifications in the frequency domain. A fundamental D_t^n operator, a generalization of integral and differential operators (differ-integration operator), is introduced as follows:

A fundamental D_t^n operator, a generalization of integral and differential operators (*differintegration* operator), is introduced as follows:

$$D_t^n = \left\{ \begin{array}{cc} \frac{d^n}{dt^n}, & n > 0 \\ 1, & n = 0 \\ \int_0^t (dA)^{-n}, & n < 0 \end{array} \right\} \tag{10}$$

where n is the fractional order and dA is a derivative function. The Laplace transform for

integral and derivative order n are, respectively:

$$L\left\{D_t^{-n} f(t)\right\} = s^{-n} F(s) \tag{11}$$

$$L\left\{D_t^{n} f(t)\right\} = s^{n} F(s) \tag{12}$$

where $F(s) = L\{f(t)\}$ and s is the Laplace complex variable. The Fourier transform can be obtained by replacing s by $j\omega$ in the Laplace transform and the equivalent frequency-domain expressions of s^n are:

$$\frac{1}{(j\omega)^n} = \frac{1}{\omega^n}\left(\cos\frac{n\pi}{2} - j\sin\frac{n\pi}{2}\right) \tag{13}$$

$$(j\omega)^n = \omega^n\left(\cos\frac{n\pi}{2} + j\sin\frac{n\pi}{2}\right) \tag{14}$$

A comprehensive tutorial in fractional calculus is given in ([20, 21]).

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References

[1] West, B., Barghava, V., and Goldberger, A. (1986). Be- yond the principle of similitude: renormalization of the bronchial tree. Journal of Applied Physiology, 60, 1089-1097.
[2] Magin, R. (2006). Fractional Calculus in Bioengineering. Begell House Publishers.
[3] Ionescu, C. (2013). The human respiratory system: an analysis of the interplay between anatomy, structure, breathing and fractal dynamics. Springer, Series in BioEngineering.
[4] Machado, J.T., Kiryakova, V., and Mainardi, F. (2013). Recent history of fractional calculus. Communications in Nonlinear Science and Numerical Simulation, 16, 1140-1153.
[5] Jacques, J. (1985). Compartmental analysis in biology and medicine.
[6] Berg, J. (2002). Biochemistry. Freeman and Company, New York.
[7] Meerschaert, M. and Sikorskii, A. (2012). Stochastic Models for Fractional Calculus. De Gruyter, Studies in Mathematics, Germany.
[8] Struys, M., De Keyser, R., and Absalom, A. (2011). Have we found the holy grail? Anesthesia and Analgesia.
[9] Schnider, T., Minto, C., Gambus, P., Andresen, C., Goodale, D., and Youngs, E. (1998). The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology, 88, 1170-1182.
[10] Schnider, T., Minto, C., Shafer, S., Gambus, P., Andresen, C., Goodale, D., and Youngs, E. (1999). The influence of age on propofol pharmacodynamicss. Anesthesiology, 90, 1502-1516.
[11] Higuchi, T. (1961). Rate of release of medicaments from ointment bases containing drugs in suspension. Journal of Pharmaceutical Sciences, 50, 874-875.
[12] Kopelman, R. (1988). Fractal reaction kinetics. Science, 241, 1620-1626.
[13] Rinaki, E., Valsami, G., and Macheras, P. (1998). The power law can describe the 'entire' drug release curve from hpmc-based matrix tablets: a hypothesis. International Journal of Pharmaceutics, 53, 749-754.
[14] Copot, D., Chevalier, A., Ionescu, C., and De Keyser, R. (2013). A two-compartment fractional derivative model for propofol diffusion in anesthesia. Conference on Systems and Control, Hyderabad, India, 28-31 August, 264-269.
[15] Ionescu, C., Copot, D., and Keyser, R.D. (2013). Three compartmental model for propofol diffusion during general anesthesia. Discontinuity, Nonlinearity and Complexity, 2, 357-368.
[16] Mortier, E., Struys, M., Smet, T.D., Versichelen, L., and Rolly, G. (1998). Closed-loop controlled administration of propofol using bispectral analysis. Anaesthesia, 53, 749-754.
[17] De Keyser, R. and Ionescu, C. (2012). A no-nonsense control engineering approach to anesthesia control during induction phase. IFAC Int Conf on Biology and Medicine, Budapest, Hungary, 379-384.
[18] De Keyser, R., Ionescu, C., and Festila, C. (2011). A one- step procedure for frequency response estimation based on switch-mode transfer function analyzer. Proceedings IEEE-CDC Conference on Decision and Control joint with ECC-European Control Conference, December 12-15, Orlando, Florida, 1189-1194.

[19] Goodwin, G., Aguero, J., Cea-Garrido, M., Salgado, M., and Yuz, J. (2013). Sampling and sampled-data models. IEEE Control Systems Magazine, 33, 34-53.
[20] Oustaloup, A. (1995). La derivation non-entiere. Hermes, Paris.
[21] Podlubny, I. (1999). Fractional differential equations. Academic Press, San Diego.